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SYMPOSIUM: THE RADIOBIOLOGY OF PARTICLE THERAPY

SP-0511
The molecular biology of particle and tissue interactions

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In contrast to energetic photons used in conventional radiotherapy, the dose delivered in particle therapy using protons and heavier ions increases as the particle penetrates the tissue and loses energy continuously. The dose therefore increases with increasing tissue thickness up to the Bragg peak which occurs near the end of the particle's range. Beyond the Bragg peak, the dose drops to zero (for protons) or almost zero (for heavier ions) so that particle therapy results in enhanced dose delivery to the target tumour and for heavier ions a dramatic increase in the ionisation density towards the end of the particle's range. Particles induce elevated levels of DNA damage in the tumour tissue cells, ultimately contributing to tumour cell death.

Predictions from biophysical models of interactions of radiation tracks with cellular DNA indicate that clustered DNA damage sites, defined as two or more lesions formed within one or two helical turns of the DNA by passage of a single radiation track, are formed in mammalian cells. These complex DNA damage sites are regarded as a signature of ionizing radiation exposure particularly as the likelihood of clustered damage sites arising endogenously is low. For instance it was predicted from biophysical modelling that ~30-40% of low LET-induced double strand breaks (DSB), a form of clustered damage, are complex with the yield increasing to>90% for high LET radiation, consistent with the reduced reparability of DSB with increasing ionization density of the radiation. The induction of radiation-induced DNA damage sites in mammalian cells has been confirmed experimentally. The increased cell killing of tumour cells has to be balanced against the increase in normal tissue damage with increasing damage complexity.

The spatial and temporal aspects of damage distribution will be discussed on the ability of ionizing radiation to produce clustered DNA damage sites,including DSB, against a plethora of endogenous damage induced and that the complexity of the clusters increases with ionization density of the radiation. It is these clustered damage sites which lead to the biological effects of ionizing radiation even for a low fluence of particle tracks. With particle radiation it is also important to consider not only delta-rays which may cause clustered damaged sites and may be highly mutagenic but the non-random spatial distribution of DSB which may lead to deletions.

In this overview I will concentrate on the molecular aspects of the variation of the complexity of DNA damage on radiation quality and the challenges this complexity presents the DNA damage repair pathways. Additionally, for heavier ions than protons, I will develop the theme of the change in ionisation density towards the end of the particle's range and how this may impact damage complexity repair and the oxygen effect. These considerations lead to increased radiobiological effectiveness.

In summary the aim is to emphasis the link between the spatial distribution of energy deposition events related to the track, the molecular products formed and the consequence of damage complexity contributing to biological effects and to present some of the outstanding molecular challenges with particle radiation.

SP-0512
Translational aspects of particle radiobiology

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Worldwide, there is an increasing interest in carbon ion radiotherapy as it allows for highly conformal treatments of deep-seated tumors due to the finite range and the in-verted depth dose profile (Bragg-curve) of charged particles. In addition, the linear energy transfer (LET) is higher in the Bragg-peak region as compared to the beam entrance region (plateau), which increases the relative biological effectiveness (RBE) towards the distal edge of the depth dose curve. The degree of conformality of charged particles is further enhanced by introducing active scanning techniques, which allow dose conformation not only at the distal but also at the proximal edge of the tumor for each field. Clinical trials have been performed in Germany and Japan, demonstrating safety and effectiveness of carbon ion radiotherapy for a variety of tumors, however a definitive confirmation that the use of carbon ions is superior to protons is still missing. Hence carbon ion therapy is presently still considered as a promising but not completely validated experimental clinical strategy.

From the radiobiological point of view, a central demand is the fact that treatment planning for carbon ions is performed in terms of RBE-weighted rather than absorbed dose. As the depth modulation for active techniques is varying throughout the complete radiation field, RBEs have to be calculated locally at each beam spot. The RBE is a complex quantity, which depends on physical parameters such as dose, LET and particle type as well as on biological properties like the tissue type and the biological endpoint. To consider the RBE in treatment planning, bio-mathematical models are required. The predictions of the RBE by these models, however, are associated with significant uncertainties, and moreover are difficult to verify in patients.

As the intention of radiotherapy to achieve complication free tumor cure can only be attained when tumor control probability and the risk of morbitity are balanced, detailed information about the impact of high-LET radiation on both, tumor and normal tissues, is of outstanding importance. For normal tissues, there exist a presently not fully understood relationship between fractionation, spatial dose distribution and the clinical outcome of radiation therapy. For tumors the questions whether high-LET irradition can overcome radiation resistance against conventional radiation strategies and which patients will benefit are most challanging. Ongoing clinical trials should therefore be accompanied by pre-clinical studies, which allow benchmarking of RBE-models for tumors and normal tissues. Beside RBE-models, these studies may also improve the understanding of the underlying mechanisms of the radiation damage and can help to assess the differential effects of high-LET treatments between tumor- and normal tissues.

In the presentation we aim to summarize the present status of clinical particle radiobiology addressing the relative biological effectiveness (RBE) and its dependencies on physical and biolological factors; show examples how RBEs for normal tissues and tumors are determined and discuss some possible underlying mechanisms possessing clinical relevance.

SP-0513
Radiobiology of charged particles and the risk of second cancers

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Radiotherapy is a common therapeutic strategy to cure cancer. The introduction of high-energy photons using electron linear accelerators has been instrumental in delivering higher doses to deep-seated tumours, while reducing the doses absorbed by the surrounding healthy tissues. Charged particle beams of protons and carbon ions have a much more favourable dose-depth distribution than X-rays and indeed protons and carbon ions are becoming widely used in radiotherapy, especially for paediatric patients.

New radiation modalities are certainly increasing local tumor control, but there is a potential for an increase in secondary cancers.The issue is now becoming of utmost importance, because the number of cancer survivors is rapidly increasing (over 10 millions in US) and the age of treatment decreasing. Thanks to the advanced treatment modalities, about 80% of children and adolescents treated for cancer become long-term survivors, but roughly 40% of them develop therapy-related morbidity. In USA, several hospitals are opening centers devoted exclusively to cancer survivors, and the NCI is supporting the Radiogenomics Consortium to study genetic predictors of late effects. EU also funded a dedicated study in the field within the 7thFP.

Mechanisms of therapy-related cancers are similar to those of sporadic tumorigenesis, but the carcinogenic potential of low doses of X-rays is not completely understood, and the uncertainty is much higher for cancer induced by charged particles. However, recent results suggest that the reduced integral dose in particle therapy may eventually largely decrease the risk of secondary cancer compared to any photon treatment. It should also be considered that the additional dose to the patient caused by concomitant diagnostic radiology, especially computed tomography, can be comparable to that caused by leakage radiation or neutrons during the treatment. Novel technological improvements may reduce the secondary dose in therapy, whilst research in genetic susceptibility should help identifying biomarkers of long-term risk in cancer survivor.